IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No.: 10/614,866 Art Unit: 1615

Filed: July 7, 2003 Examiner: Lakshmi Sarada Channavajjala

For: *ABUSE-DETERRENT PHARMACEUTICAL COMPOSITIONS OF OPIOIDS AND OTHER DRUGS*

Commissioner for Patents
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DECLARATION UNDER 37 C.F.R. 1.132

Sir:

I, Alison B. Fleming, hereby declare:

1. I am a co-inventor of the above-identified patent application.

2. I have read the office action mailed March 29, 2007, and participated in the interview with the Examiner on April 23, 2007.

3. As discussed in the interview, our method produces a material which is more resistant to abuse by extraction of the active agent, such as oxycodone, from the carrier, than known available formulations. This is distinct from a formulation that is more resistant to abuse due to differences in the active ingredient or dosage. Our invention is to incorporate a lipophilic drug or lipophilic derivative of a drug into a wax, fatty acid or

similar material, from which it is difficult to extract, then incorporate the active-dispersed lipid carrier in a standard pharmaceutical excipient formulation.

4. Oshlack (6,696,088) teaches hydrophobic materials such as waxes, fatty acids etc (col 28, L18-54) in combination with other excipients to form sustained release dosage forms. However, formulation of a drug in such excipients is not sufficient to produce a dosage form that prevents the immediate release of a substantial portion of the drug when the dosage form is crushed or chewed and exposed to an aqueous medium. The following example is intended to illustrate the formulation and functional differences between the claimed formulations and compositions of Oshlack.

5. Preparation of Abuse Resistant Granules Containing Oxycodone

Ingredient	Amount used to formulate Lot NB022-93	Amount used to formulate Lot NB022-96	Amount used to formulate Lot NB066-44	Amount used to formulate Lot NB066-67
Oxycodone Base	5g	5g	10g	5g
Myristic Acid	--	--	50g	30g
Stearic Acid	34g	34g	--	--
Yellow Beeswax	10g	--	10g	10g
Carnauba wax	5g	10g	20g	10g

Procedure:

1. Fatty acid (myristic or stearic acid) was melted in an erlenmeyer flask in a silicone oil bath at 100°C. Note the composition was subjected to stirring and was kept under an argon blanket for this and all subsequent steps.

2. Oxycodone base was introduced into the molten fatty acid and the melt was stirred until all oxycodone base dissolved and a clear liquid was formed.

3. Yellow beeswax was added and melted under constant stirring.

4. Carnauba wax was added and melted under constant stirring.

5. The resulting homogeneous molten solution was poured onto aluminum foil and allowed to solidify at room temperature.

6. The bulk wax obtained was combined with dry ice and subjected to size reduction in a mortar and pestle.

7. The dry ice was allowed to dissipate and the particles were sieved to obtain various size ranges. Particles 20-40 mesh in size (400-841 micron) were subjected to testing.

6. Marketed formulation of Oxycodone

A marketed formulation of oxycodone, Oxycontin®, was tested in order to illustrate the properties of the formulations described in Oshlak et al. Oxycontin® is the closest available marketed formulation to that described in Oshlack. The table below outlines the ingredients in the marketed formulation as compared to the ingredients in Examples 6, 7, 11, and 12 of U.S. Patent No. 6,696,088 to Oshlak et al.

Oxycodone formulation similar to Oshlak, et al.

Ingredient	Present in Oxycodone HCl Controlled Release Tablets of Examples 6, 7, 11 and 12 of US 6,696,088	Present in Oxycontin®
Oxycodone HCl	X	X
Lactose	X	X
Povidone	X	X
Eudragit RS 30D (ammonio methacrylate copolymer)	X	X
Triacetin	X	X
Stearyl Alcohol	X	X
Talc	X	X
Magnesium Stearate	X	X
Naltrexone HCl Beads	X	-
Opadry Pink (Hypromellose, titanium dioxide, polyethylene glycol 400)	X	X
Sodium Hydroxide	-	X
Sorbic Acid	-	X

The table above demonstrates that the formulation described in Oshlak is very similar to the commercially available Oxycontin® tablet. The primary difference is that Oxycontin® does not contain an antagonist (Naltrexone HCl).

7. Tampering Simulation

A tampering simulation was conducted on Abuse Resistant Granules (see 5 above) and on Oxycontin® tablets (see 6 above). Oxycontin® was used to illustrate the properties of a formulation prepared as per the Examples in Oshlak.

Granules or tablets were crushed using a glass mortar & pestle. The resulting crushed material was placed in a dissolution vessel equipped with paddles (USP Apparatus II). 900 mL of 0.1N HCl pre-warmed to 37°C was added to the vessels and stirring was conducted for 15 minutes. After 15 minutes the amount of oxycodone released was determined. See table below for results.

Amount of Oxycodone Released in Dissolution/Tampering Study

Sample	% Released in 15 minutes in 0.1N HCl (n=3)
Oxycontin® (40 mg Tablet)	95.6 +/-2.7
NB022-93 (granules containing 40 mg oxycodone HCl equivalent)	31.6 +/- 2.6
NB022-96 (granules containing 40 mg oxycodone HCl equivalent)	19.7 +/- 1.4
NB066-44 (granules containing 20 mg oxycodone HCl equivalent)	14.8 +/-1.1
NB066-67 (granules containing 20 mg oxycodone HCl equivalent)	18.2 +/- 1.6

8. Conclusion

Granules were produced by dispersing a lipophilic derivative of oxycodone (oxycodone base) in a carrier consisting of water insoluble, waxy excipients (fatty acids, carnauba and beeswax). When crushed, these granules released approximately 32% or less of their drug load when exposed to 0.1N HCl for 15 minutes. In contrast, a formulation which was very close to the examples outlined in U.S. Patent No. 6,696,088

to Oshlak et al. released approximately 96%. This example illustrates formulation and functional differences between the claimed formulations and compositions of Oshlack.

9. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 6/29/07

Alison B. Fleming

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